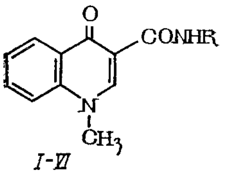
AMIDES OF N-METHYL-4-QUINOLONE-3-CARBOXYLIC ACID

I. A. Kozello, V. I. Khmelevskii,
and A. Ya. Gasheva

UDC 615.216 : 547.585.012.1 : 542.9

The synthesis of some amides of N-methyl-4-quinolone-3-carboxylic acid (II-VI) is described:



I-VI

The study of N-methyl-4-quinolone-3-carboxylic acid derivatives is of interest because compounds of this type are based on a skeleton of a molecule of N-methyl-γ-quinolone: the alkaloid echinopsine, which is one of the effective neuromuscular stimulants [1-2].

Synthesis of the compounds (see Table 1) was accomplished by the reaction of ethyl N-methyl-4-quinolone-3-carboxylate with ammonia or with another compound containing the amino group (hydrazine hydrate, cyclohexylamine [3], N-phenylpropanediamine-1,3 [4], β-piperidino- and β-morpholinoethylamines [5, 6]).

The ethyl N-methyl-4-quinolone-3-carboxylate required for the synthesis of these compounds was prepared by methylation of ethyl 4-hydroxyquinoline-3-carboxylate with methyl iodide in dimethylformamide in the presence of potassium carbonate [7].

The investigation of the effect of the compounds prepared on neuromuscular conductivity showed that they are less active than N-methyl-4-quinolone-3-carboxylic acid itself, reacting like the alkaloid echinopsine.

EXPERIMENTAL

Amide of N-Methyl-4-quinolone-3-carboxylic Acid (I). A mixture of 1 g of ethyl N-methyl-4-quinolone-3-carboxylate and 25 ml of 24% aqueous ammonia was heated at 70-90°C for 5 h. During this time a further 25 ml of the same ammonia solution was added. After cooling, the precipitate was filtered off, washed with water, dried, and recrystallized from alcohol or water. Yield was 75%, mp 276-278°C.

Hydrazine of N-Methyl-4-quinolone-3-carboxylic Acid (II). A mixture of 2.85 g of ethyl N-methyl-4-quinolone-3-carboxylate and 1.25 g of hydrazine hydrate in 40 ml of absolute alcohol was boiled on a water bath for 2.5 h. After evaporation of the alcohol, the residue (1.7 g) was recrystallized from 50 ml of water. Yield was 66%, mp 250-252°C.

Cyclohexylamide of N-Methyl-4-quinolone-3-carboxylic Acid (III). A mixture of 1 g of ethyl N-methyl-4-quinolone-3-carboxylate and 0.5 g of cyclohexylamine was boiled for 3.5 h, then cooled slowly to room temperature, and 10-15 ml of water was added.

The precipitate, well-triturated under water, was filtered off, washed with water, and dried. After several recrystallizations from aqueous alcohol (1 : 1) a product with mp 200-202°C was obtained. Yield was 70%.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Ural Branch, Sverdlovsk. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 5, No. 1, pp. 24-26, January, 1971. Original article submitted March 23, 1970.

TABLE 1. Amides of N-Methyl-4-quinolone-3-carboxylic Acid

Compound	NHR	Found (in %)			Empirical formula	Calculated (in %)		
		C	H	N		C	H	N
I	NH_2	65,47 65,07	5,12 5,14	13,72 13,85	$C_{11}H_{10}N_2O_2$	65,33	4,98	13,86
II	$NHNH_2$	60,73 60,63	5,08 5,11	19,12 19,51	$C_{11}H_{11}N_3O_2$	60,77	5,10	19,35
III	NHC_6H_{11}	71,88 72,00	7,15 7,21	9,58 10,11	$C_{17}H_{20}N_2O_2$	71,80	7,09	9,85
IV	$NHCH_2CH_2CH_2NHC_6H_5$	71,79 72,14	6,38 6,36	12,38 12,59	$C_{20}H_{21}N_3O_2$	71,61	6,31	12,53
V	$NHCH_2CH_2\overline{N(CH_2)_4CH_2}$	68,94 68,82	7,38 7,37	13,10 13,10	$C_{18}H_{23}N_3O_2$	68,98	7,39	13,40
VI	$NHCH_2CH_2\overline{N(CH_2)_2OCH_2CH_2}$	64,65 64,98	6,66 6,69	13,34 13,01	$C_{17}H_{21}N_3O_3$	64,74	6,71	13,32

γ-Phenylaminopropylamide of N-Methyl-4-quinolone-3-carboxylic Acid (IV). A mixture of 1 g of ethyl N-methyl-4-quinolone-3-carboxylate and 0.75 g of N-phenylpropanediamine-1,3 was boiled for 3 h and cooled to room temperature, and the liquid melt obtained was triturated under water. The precipitate was filtered off, washed, and dried. Yield was 0.9 g (55%), mp 148-149°C (from ethanol).

β-Piperidinoethylamide of N-Methyl-4-quinolone-3-carboxylic Acid (V). A mixture of 1.15 g of ethyl N-methyl-4-quinolone-3-carboxylate and 1.3 g of β-piperidinoethylamine was boiled at 175-180°C for 25 h. It was cooled to room temperature and triturated under water; the compound which crystallized was filtered off and washed with distilled water. Recrystallization of 1.5 g of the dry product from 15 ml of aqueous alcohol yielded 1 g (66.6%) of a compound with mp 121-123°C.

β-Morpholinoethylamide of N-Methyl-4-quinolone-3-carboxylic Acid (VI). A mixture of 1.15 g of ethyl N-methyl-4-quinolone-3-carboxylate and 1.3 g of β-morpholinoethylamine was boiled for 25 h; then the melt was cooled and triturated adding 15 ml of distilled water. This yielded a crystalline product which was filtered off, washed, and dried. Recrystallization of 1 g of the dry product from 4 ml of absolute alcohol yielded 0.7 g (44.8%) of compound with mp 165-167°C.

LITERATURE CITED

1. G. P. Gubina, Med. Prom. SSSR, No. 2, 53 (1960).
2. M. D. Mashkovskii, Medicinal Remedies [in Russian] (1960), p. 108.
3. A. Baeyer, Justus Liebigs Ann. Chem., 278, 102 (1894); Hideo Nagano, Chem. Abstr., 55, 11413f (1961).
4. A. F. Bekhli, Zhur. Obshch. Khim., 19, 1555 (1949).
5. F. Cornet et al., Chem. Abstr., 61, 8276 (1964).
6. M. Zehmann, Ber. Dtsch. Chem. Ges., 27, 2177 (1894).
7. F. F. Duffin and J. D. Kendall, J. Chem. Soc., 1948, 893; Brit. Pat. No. 820,295; Chem. Abstr. 54, 8862 (1960).